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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,113	04/09/2001	William Edward Evans	44158/209598 (5853-3)	2302

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 07/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/829,113

Applicant(s)

EVANS ET AL.

Examiner

Jeffrey Fredman

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 8, 2003 has been entered.

Status

Claims 1-18 are pending.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-16, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) and further in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843).

Li teaches a method of determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism and a second nucleotide polymorphism (see page 360, figure 1) comprising:

(a) obtaining a DNA sample from a human source comprising said contiguous DNA segment (page 358, column 1),

(b) using said DNA sample as a template for polymerase chain reaction amplification of a DNA fragment to form a product which is capable of being subject to intramolecular ligation (page 358, column 2, subheadings "GPA-specific PCR" and page 360, figure 1),

wherein the PCR amplification is performed with

(i) a first primer capable of annealing to a region adjacent to the first NP and distal to the second NPs (see figure 1, where the MN-FP primer is adjacent to the 5' G/T polymorphism and distal from the 3' G/T, C/A/G and C/T polymorphisms)

(ii) a second primer capable of annealing to a region adjacent to the second NP and distal to the first NP (see figure 1, where the MN-CR primer is adjacent to the 3' G/T, C/A/G and C/T polymorphisms and distal from the 5' G/T polymorphism),

(c) ligating the ends of the DNA fragment to each other so as to produce a circular DNA molecule (page 358, subheading "ligation of the amplified fragment" and page 360, figure 1),

(d) determining the haplotype of the first and second nucleotide polymorphism by allele specific inverse PCR amplification (page 358, subheading "Allele specific PCR" and page 360, figure 1).

With regard to claims 5-8, Li teaches first, second and third NPs that are single nucleotide substitutions with some NPs located between the end NPs whose haplotype is determined (see figure 1, page 360).

With regard to claim 9, Li teaches use of human sources (see page 358, column 1).

With regard to claim 13, Li teaches that the primers are allele specific (see page 360, figure 1).

With regard to claims 14-16, Li teaches determination of each allele of the clinically relevant Glycophorin gene (see page 358, column 1 and page 360, figure 1).

With regard to claims 21 and 22, Li teaches a DNA sequence immediately adjacent to the 5' and 3' NPs which is less than 50 bases long.

Li suggests the use of the method on haplotyping distances that are too long to be PCR amplified (see page 361, column 1).

While Li suggests applying the method to situations with polymorphisms that are distant from one another, Li does not exemplify application of the method to sequences which are 200 to 30,000 bases apart nor the use of long range PCR.

Regarding claim 1 and dependent claims 2-4, Patel teaches that inverse PCR methods such as those used by Li can be applied to haplotype sequences up to 10 kb apart and suggests that even larger regions can be used (page 3567, column 1, lines 6-9).

Regarding claims 11 and 12, Patel teaches restriction digestion to enhance inverse PCR and detection with such digestion (see page 3562, column 1 and page 3563, figure 2)

Patel teaches mutations which are substitutions of single nucleotides and where there are a series of nucleotide polymorphisms located between the two amplified polymorphisms (see page 3561, column 2 and page 3562, figure 1). Patel teaches determining the presence of multiple different polymorphisms (see page 3565, column 1, subheading "Double ARMS Inverse PCR (DARMSI-PCR)". Patel teaches amplification and detection of each haplotype in the same gene, the globin cluster (page 3562, figure 1). Patel further teaches that the method can be used for diagnostic purposes (see page 3567, column 1).

Michalatos-Beloin teaches haplotyping methods where the molecules are prepared by long range PCR (page 4842, figures 2 and 3). Michalatos-Beloin also teaches that amplification of up to 40 kb should be possible (see page 4843 (listed as page 4867), column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the long range PCR method of Michalatos-Beloin to amplify the sample of Li since Michalatos-Beloin states "The allele-specific long range

PCR products were used as templates for amplification of the STR (page 4867, column 1)". An ordinary practitioner would have been motivated to use long range PCR to prepare the template for the method of Li in order to extend the range of detection of polymorphisms in order to solve the problem of Li that there are "polymorphisms separated by a distance that is too long to be amplified by PCR (see page 361, column 1)." Li recognizes the problem in that some haplotypes are too distant to be amplified by standard PCR. Michalatos-Beloin solves the problem using long range PCR.

Further, Michalatos-Beloin notes "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications (page 4867, column 2). Thus, application of the method of Michalatos-Beloin to the inverse PCR method of Li can be used to increase the accuracy of the Li method. Further motivation to apply the Michalatos-Beloin method to Li is provided by Patel, who teaches that haplotyping using inverse PCR is desirable on long segments, even haplotypes separated by more than 10,000 nucleotides (see page 3567, column 1). This represents further motivation to apply the method of Li to more widely separated polymorphisms, as well as teachings on how to perform that method.

4. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res. (1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Krynetski et al (Proc. Natl. Acad. Sci. (1995) 92:949-953).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above. Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the TPMT gene.

Krynetski teaches that there are two haplotypes in the TPMT gene, one of which is associated with cytotoxicity in chemotherapeutic treatment using methylmercaptapurine (see page 949, columns 1 and 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the TPMT gene since Krynetski teaches "Identification of the inactivating mutations at the TPMT locus would not only provide important insights into the molecular mechanisms of this genetic polymorphism but might also offer a method of prospectively identifying heterozygotes and TPMT-deficient patients prior to treatment with potentially toxic dosages of mercaptopurine (page 949, column 2)". Thus, an ordinary practitioner would have been motivated to haplotype the TPMT gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are TPMT deficient prior to toxic treatment.

5. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel et al (Nucleic Acids Research (1991) 19:3561-3567) in view of Michalatos-Beloin et al (Nucleic Acids Res.

(1996) 24:4841-4843) as applied to claims 1-16, 21 and 22 and further in view of Martin et al (Am. J. Hum. Genet. (2000) 67:383-394).

Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin teach the limitations of claims 1-16, 21 and 22 as discussed above. Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin do not teach application of the method to the listed genes.

Martin teaches haplotype analysis of the ApoE gene in order to analyze the presence of Alzheimer's disease (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Li et al (Biotechniques (1998) 25(3): 358, 360, 361) in view of Patel in view of Michalatos-Beloin to haplotype the ApoE gene since Martini teaches "Haplotype analysis using family data increased significance over that seen in single-locus tests for some of the markers, and for these data, improved localization of the gene (abstract)." Thus, an ordinary practitioner would have been motivated to haplotype the ApoE gene using the method of Patel in view of Michalatos-Beloin, where Patel teaches that the method is useful "for routine diagnostic purposes (page 3567, column 1)", in order to diagnose patients who are at risk for Alzheimer's disease.

Response to Arguments

6. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Specifically, the new Li reference (surprisingly hard to find) teaches the limitation that was newly added to overcome the previous rejection (and which did overcome the previous rejection).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Jeffrey Fredman
Primary Examiner
Art Unit 1634

July 3, 2003